REMARKS

This is a response to the Final Office Action mailed on January 5, 2011. The Commissioner is hereby authorized to charge for any fees that may be required or credit any overpayment to Deposit Account No. 02-1818. If such a withdrawal is made, please indicate the Attorney Docket No. 3712036-00697 on the account statement.

Claims 1, 4, 5 and 7-13 are rejected in the application. Claims 2, 3, and 6 were previously canceled without disclaimer. In the Office Action, Claims 1, 4, 5 and 7-12 are rejected under 35 U.S.C. §112; and Claim 13 is rejected under 35 U.S.C. §103(a). In response, Claim 5 has been amended, and Claims 14-22 have been added. The amendments do not add new matter. In view of the amendments and/or for at least the reasons set forth below, Applicants respectfully submit that the rejections be reconsidered and withdrawn.

New Claims 14-22 are submitted herewith. Support for these new claims can be found, for example, at paragraph [0028] to [0030] of Applicants' specification. New Claims 14-22 have been added to recite specific protein sources, lipid sources, and carbohydrate sources. Applicants respectfully submit that new Claims 14-22 are definite under 35 U.S.C. §112 and novel and non-obvious over any prior art. Accordingly, Applicants respectfully request that Claims 14-22 be allowed.

In the Office Action, Claims 1, 4, 5 and 7-12 are rejected under 35 U.S.C. §112, ¶2 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Patent Office asserts that "the terms 'protein source,' 'lipid source,' and 'carbohydrate source' render the claims indefinite because it is unclear what is the scope of these terms." See, Office Action, page 3, lines 7-8. Applicants respectfully disagree for at least the reasons set forth below.

Independent Claim 1 recites, in part, a method for treating and/or improving insulin resistance by reducing insulin resistance, the method comprising administering to a patient having reduced insulin sensitivity a nutritional and/or pharmaceutical product comprising lactulose in an amount from about 0.2 to about 90% by total weight of the product, a protein source in an amount from about 21 to about 40% of the total weight of the product, a lipid source in an amount from about 5% to about 40% of the total weight of the product, and a carbohydrate source in an amount that is less than 10% by weight of the product.

Independent Claim 5 recites, in part, methods for treating and/or improving insulin resistance comprising administering to a patient a composition comprising lactulose, a protein source in an amount from about 21 to about 40% of the total weight of the product, a lipid source in an amount from about 5% to about 40% of the total weight of the product, and a carbohydrate source in an amount that is less than 10% by weight of the product. The lactulose is administered in an amount of from 0.1 to 1.5g per kg body weight.

The standard for determining whether the definitiveness requirement is met under 35 U.S.C. § 112, ¶2 is "whether those skilled in the art would understand what is claimed when the claim is read in light of the Specification." *Orthokinetics Inc. v. Safety Travel Chairs Inc,* 1 U.S.P.Q. 2d 1081-1088 (Fed. Cir. 1986). "If the claims, read in light of the Specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the Courts can demand no more." *North American Vaccine Inc. v American Cyanamid Co.,* 28 U.S.P.Q. 2d 1333, 1339 (Fed. Cir. 1993). By statute, 35 U.S.C. 112, Congress has placed no limitations on how an applicant claims his invention, so long as the specification concludes with claims which particularly point out and distinctly claim that invention." *In re Pilkington,* 162 U.S.P.Q. 145, 148 (C.C.P.A. 1996).

Applicants respectfully submit that the specification provides guidance to the skilled artisan in making a determination of what sort of ingredient to add to the nutritional or pharmaceutical product in the claims to act as protein, carbohydrate, and lipid sources. The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art." *Ex parte Hiyamizu,* 10 U.S.P.Q. 2d 1393, 1394 (Bd. Pat. App. & Inter. 1988). The person of ordinary skill in the art is "also a person of ordinary creativity, not an automaton." *KSR v. Teleflex,* 82 USPQ2d 1385, 1397 (2007). The skilled artisan creating the claimed nutritional or pharmaceutical product would be capable of understanding basic principles of biology, biochemistry and metabolism and would be able to apply some common sense and creativity when reading the words "carbohydrate source," protein source," and "lipid source." The skilled artisan would be able to make a reasonable inference based on the examples of carbohydrate, protein, and lipid sources in the specification that "source" would not be any ingredient that through multiple metabolic pathways may provide a component of a protein, lipid

or carbohydrate, but would rather be something from which carbohydrates, proteins, and lipids may be easily derived. For example, the specification lists as example protein sources: sweet whey, pea protein, and soy proteins. See, specification, page 7, lines 6-7. The examples provide full proteins for digestion in the body, not something that after extensive metabolism through multiple pathways may yield a component of a protein. From the context given in the specification, the skilled artisan would be able to apply reasonable inferences and ordinary creativity to ascertain what types of ingredients would act as "sources" in the context of the claims.

The skilled artisan would recognize that the traditional usage of the word "source" in the context of the claims would be something that provides all, or at least, key components of proteins, lipids, and carbohydrates. The Patent Office suggests that a "source" is overly broad because a carbohydrate may be metabolized to glucose which through another metabolic pathway could be used to make amino acids which could then be used to make proteins. See, Office Action, page 3, lines 11-15. That is not though how a skilled artisan would interpret the word. A source should provide at least the crucial component, that without which an ingredient would not be a protein, lipid, or carbohydrate. A protein must include amino acids, regardless of whatever cofactors may also be bonded to it. Similarly, a lipid must comprise fatty acids or steroids, and a carbohydrate is made of mono and/or polysaccharides.

The Patent Office argues that, for example, that glucose could be a protein source and that glucose's lack of nitrogen necessary for the formation of an amino acid is rectified by other metabolic pathways providing nitrogen. See, Office Action, page 4, lines 6-8. Applicants respectfully disagree. There would be no reason for a skilled artisan to assume a source of a protein is something that can, as admitted by the Patent Office, never be directly converted to amino acids and thereby form a protein In that case, the glucose is not acting as a "protein source." The exogenous ingredient in the composition is not providing a source for a protein. The body itself, through multiple metabolic steps unrelated to the supplementation of the composition in the present claims provides the necessary components to create a protein. Because the addition of glucose as a carbohydrate source to the composition does not in itself provide all the necessary components for protein formation, it cannot be considered to be a

"protein source." In contrast, the glucose is a carbohydrate and does directly provide carbohydrates to the body.

The Patent Office suggests that the skilled artisan would not know whether something was a carbohydrate source or a lipid or protein source. Common usage of these terms provides evidence that they, to a skilled artisan, refer to different types of ingredients. For example, the skilled artisan may be presumed to be at least reasonably familiar with the basics of biochemistry and nutrition. An introductory textbook on biochemistry discusses sources of carbohydrates in a table. The table includes, for example, potatoes, table sugar, and bread. See, THOMAS DEVLIN (ed.), TEXTBOOK OF BIOCHEMISTRY WITH CLINICAL CORRELATIONS, (4th ed), 1074, t. 26.7 (1997), attached as Exhibit A. None of the listed dietary sources require multiple metabolic pathways and the endogenous production of other components in order to provide carbohydrates to the body. Also, that same introductory textbook discusses the difference between high carbohydrate and high fat diets without a definition of what sorts of ingredients would be used for each diet. The discussion presumes that the reader has the requisite skill and knowledge to be able to clearly distinguish an ingredient high in carbohydrates acting as a carbohydrate source from one high in fats acting as a lipid source. See, THOMAS DEVLIN (ed.), TEXTBOOK OF BIOCHEMISTRY WITH CLINICAL CORRELATIONS, (4th ed), 1096 (1997), attached as Exhibit A. The skilled artisan ought to be able to do the same when interpreting the present claims and conclude easily what is a lipid source, a protein source, or a carbohydrate source.

With respect to the Patent Office's assertion that the word "source" may also be interpreted to "encompass non-metabolic organic synthesis reactions" as well as "metabolic conversion of compounds" (see, Office Action, page 4, lines 11-13), Applicants respectfully disagree. As discussed above, construed in light of the specification, the skilled artisan would know from the other types of ingredients or components used in the composition to which the present claims are directed which type of source, be it organic or inorganic, would be most appropriate to use in the composition.

In sum, the source would be interpreted by the person of ordinary skill in the art as the provider of the most crucial component, if not the provider of all the components of a particular ingredient; here, a carbohydrate, lipid, or protein. Based on at least these noted reasons, Applicants believe that Claims 1, 4, 5 and 7-12 fully comply with 35 U.S.C. §112, second

paragraph. Accordingly, Applicants respectfully request that the rejection of Claims 1, 4, 5 and 7-12 under 35 U.S.C. §112 be withdrawn.

In the Office Action, Claim 13 is rejected under 35 U.S.C. §103(a) as being unpatentable over Diab. Nutr. Metab. 1992, 5, p295-297 to Genovese et al. ("*Genovese*") in view of J. Clin. Invest. 1985, 75, pages 608-613 to Florent et al. ("*Florent*"). Applicants respectfully traverse the rejection for at least the reasons set forth below.

Independent Claim 13 recites, in part, methods for treating and/or improving insulin resistance by administering to a patient in need of same an effective amount of a composition comprising lactulose, wherein the composition is administered between 3 and 7 hours before a meal. Surprisingly, the present inventors have found that acetogenic fibers have significant effects in improving insulin sensitivity, and in particular, in reestablishing normal insulin sensitivity and thus a normal systemic metabolism. See, specification, page 4, lines 15-17. Without wishing to be bound to any theory it is presently assumed that an increased amount of acetate in blood and tissues – resulting from an administration of a composition according to the present invention results in reduced lipolysis, *i.e.*, a reduced liberation of glycerol and fatty acids from tissues into the blood. This could result in a reduction in the amount of free fatty acids inactivating insulin receptors, which, in turn, could result in an improvement in insulin sensitivity even to the levels present in healthy persons. See, specification, page 5, lines 17-22. In contrast, Applicants submit that the cited references are deficient with respect to independent Claim 13.

Genovese and *Florent* alone or in combination fail to disclose or suggest administering to a patient in need of reduced insulin resistance an effective amount of a composition comprising lactulose as required by independent Claim 13. *Genovese* and *Florent* alone or in combination also fail to disclose or suggest administering to a patient in need of reduced insulin resistance an effective amount of a composition comprising lactulose between 3 and 7 hours before a meal as required by independent Claim 13.

The Patent Office alleges that *Genovese* teaches the method of treating insulin resistance by reducing insulin resistance because "Genovese et al. teaches a reduction of blood glucose with no significant difference in serum insulin concentration in non-insulin dependent diabetic patients…suggesting a reduction of resistance to the same level of insulin." See, Office Action,

page 6, lines 11-16. Applicants respectfully suggest that the Patent Office has mischaracterized the result in *Genovese*. Insulin resistance is accurately measured by examining the fasting glucose to insulin ratio. See, *e.g.* Richard S. Legro et al., *A Fasting Glucose to Insulin Ratio is a Useful Measure of Insulin Sensitivity in Women with Polycystic Ovary Syndrome*, J Clin Endocrinol Metab. 1998 Aug; 83(8):2694-8, attached as Exhibit B. *Genovese* found that the administration of purified lactulose "did not exert any significant influence on fasting blood glucose." See, *Genovese*, page 296, Results, paragraph 3. *Genovese* also showed that "fasting...serum insulin concentrations did not show any significant difference." See, *Genovese*, page 296, Results, paragraph 5. Together, this means that lactulose did not change the fasting glucose to insulin ratio, meaning that the level of insulin resistance expressed by the subject was not affected. There are multiple physiological processes that can affect blood gluocose levels without affecting insulin resistance. It is one of those other processes that is disclosed in *Genovese*. The researchers attribute the effect on blood glucose to lactulose's effect on hepatic glucose production. See, *Genovese*, page 296, Discussion, paragraphs 2-3. Therefore, *Genovese* does not teach a method of treating insulin resistance by reducing insulin resistance. *Florent* does not teach such a method either. *Florent* is entirely directed to studies to investigate the effects of a repeated load of an unabsorbable carbohydrate on the intracolonic metabolism (including H2 production) of this sugar. See, *Florent*, page 608, column 2, first full paragraph. Therefore, *Genovese* and *Florent*, either alone or in combination, fail to disclose or suggest treating and/or improving insulin resistance by reducing insulin resistance in accordance with independent Claim 13.

For at least the reasons set forth above, Applicants respectfully submit that the cited references fail to disclose or suggest each and every element of independent Claim 13. Moreover, the cited references fail to even recognize the advantages, benefits and/or properties of treating and/or improving insulin resistance by reducing insulin resistance in accordance with independent Claim 13. As a result, independent Claim 13 is novel and non-obvious over the cited art.

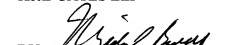
Accordingly, Applicants respectfully request that the obviousness rejection of Claim 13 be reconsidered and withdrawn.

For the foregoing reasons, Applicants respectfully request reconsideration of the above-

identified patent application and earnestly solicit an early allowance of same. In the event there remains any impediment to allowance of the claims which could be clarified in a telephonic interview, the Examiner is respectfully requested to initiate such an interview with the undersigned.

Respectfully submitted,

K&L GATES LLP

BY 

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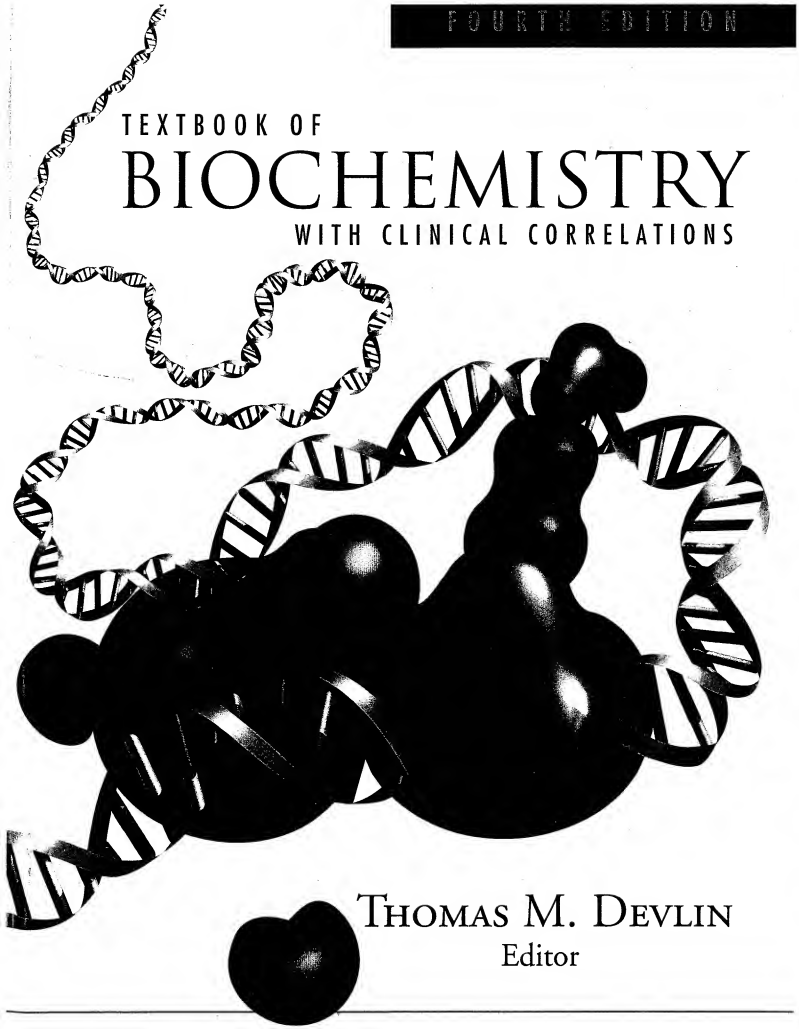
Dated: March 30, 2011

EXHIBIT A

FOURTH EDITION

TEXTBOOK OF BIOCHEMISTRY

WITH CLINICAL CORRELATIONS



THOMAS M. DEVLIN
Editor

TABLE 26.7 Dietary Carbohydrates

Carbohydrate	Typical Source	Structure
Amylopectin	Potatoes, rice, corn, bread	α-Glc(1 → 4)$_n$Glc with α-Glc(1 → 6) branches
Amylase	Potatoes, rice, corn, bread	α-Glc(1 → 4)$_n$Glc
Sucrose	Table sugar, desserts	α-Glc(1 → 2)β-Fru
Trehalose	Young mushrooms	α-Glc(1 → 1)α-Glc
Lactose	Milk, milk products	β-Gal(1 → 4)Glc
Fructose	Fruit, honey	Fru
Glucose	Fruit, honey, grape	Glc
Raffinose	Leguminous seeds	α-Gal(1 → 6)α-Glc (1 → 2)β-Fru

Hydrated starch and glycogen are attacked by the endosaccharidase **α-amylase** present in saliva and pancreatic juice (Figure 26.24). Hydration of the polysaccharides occurs during heating and is essential for efficient digestion. Amylase is specific for internal α-1,4-glucosidic bonds; α-1,6 bonds are not attacked, nor are α-1,4 bonds of glucose units that serve as branch points. The pancreatic isoenzyme is secreted in large excess relative to starch intake and

CLINICAL CORRELATION 27.4

Carbohydrate Loading and Athletic Endurance

The practice of carbohydrate loading dates back to observations made in the early 1960s that endurance during vigorous exercise was limited primarily by muscle glycogen stores. Of course, the glycogen stores are not the sole energy source for muscle. Free fatty acids are present in the blood during vigorous exercise and are utilized by muscle along with the glycogen stores. Once the glycogen stores have been exhausted, however, muscle cannot rely entirely on free fatty acids without tiring rapidly. This is probably related to the fact that muscle becomes partially anaerobic during vigorous exercise. While glycogen stores are utilized entirely well aerobically or anaerobically, fatty acids can only be utilized aerobically. Under those conditions, fatty acids cannot provide ATP rapidly enough to serve as the sole energy source.

Thus the practice of carbohydrate loading to increase glycogen stores was devised for track and other endurance athletes. Originally, it was thought that it would be necessary to trick the body into increasing glycogen stores. The original carbohydrate loading regimen consisted of a 3–4-day period of heavy exercise followed by a low-carbohydrate diet, followed by 1–2 days of light exercise while on a high-carbohydrate diet. The initial low-carbohydrate–high-energy demand period caused a depletion of muscle glycogen stores. Apparently, the subsequent change to a high-carbohydrate diet resulted in a slight rebound effect, with the production of higher than normal levels of insulin and growth hormone. Under these conditions glycogen storage was favored and glycogen stores reached almost twice the normal amounts. This practice did increase endurance significantly. In one study, test subjects on a high-fat and high-protein diet had their stores of glycogen per 100 g of muscle and could perform a workload for only 60 min. When the same subjects were on a high-carbohydrate diet for 3 days, their glycogen stores rose to 4 g per 100 g of muscle and the same workload could be performed for up to 4 h.

While the technique clearly worked, the athletes were lethargic and irritable during the low-carbohydrate portion of the regimen, and the high-fat diet ran counter to current recommendations. Fortunately, recent studies show that the consumption of a high complex-carbohydrate diet during training increases glycogen stores without the great stress on the body with sudden dietary changes. Current recommendations are for endurance athletes to consume a high carbohydrate diet (with emphasis on complex carbohydrates) during training. The carbohydrate intake is increased further (to 70% of calories) as exercise tapered off during the 2–3 days just before the athletic event. This procedure increases muscle glycogen stores to levels comparable to the original carbohydrate loading regimen.

Conlee, R. K. Muscle glycogen and exercise endurance: a twenty-year perspective. *Exerc. Sport Sci. Rev.* 15:1, 1987; Ivy, J. L., Costill, D. L., Fink, C. L., Sherman, W. M., and Coyle, E. F. Muscle glycogen storage after different amounts of exercise: effect of time of carbohydrate ingestion. *J. Appl. Physiol.* 48:1076, 1988; and Probart, C. K., Bird, P. J., and Parker, K. A. Dietary practices and performance. *Med. Clin. North Am.* 77:757, 1993.

CLINICAL CORRELATION 27.5

High-Carbohydrate Versus High-Fat Diets for Diabetics

For years the American Diabetes Association has recommended diets that were low in fat and high in complex carbohydrates and fiber for diabetics. The logic of such a recommendation seemed inescapable. Diabetics are prone to hyperlipidemia with the attendant risk of heart disease, and low-fat diets appeared likely to reduce risk of hyperlipidemia and heart disease. In addition, numerous clinical studies had suggested that the high-fiber content of these diets resulted in improved control of blood sugar. This recommendation has proved to be controversial. An understanding of the controversies involved illustrates the difficulties in making dietary recommendations for population groups rather than individuals. In the first place, it is very difficult to make any major changes in dietary composition without changing other components of the diet. In fact, most of the clinical trials of the high-carbohydrate–high-fiber diets have resulted in significant weight reduction, either by design or because of the lower caloric density of the diet. Since weight reduction improves diabetic control, it is not entirely clear whether the improvements seen in the treated groups were due to the change in diet composition *per se* or because of the weight loss. Second, there is significant individual variation in how diabetics respond to these diets. Many diabetic patients appear to show poorer control (as evidenced by higher blood glucose levels, elevated VLDL and/or LDL levels, and reduced HDL levels) on the high-carbohydrate–high-fiber diets than on diets high in monounsaturated fatty acids. However, diets high in monounsaturated fatty acids tend to have higher calorie density and are inappropriate for overweight individuals with type II (non-insulin dependent) diabetes. Thus a single diet may not be entirely appropriate for all diabetics. Even the "glycemic index" concept (Table 27.2) may also turn out to be difficult to apply to the diabetic population as a whole, because of individual variation. Thus, in 1994 the American Diabetes Association abandoned the concept of a single diabetic diet. Instead, their recommendations focus on achievement of glucose, lipid, and blood pressure goals via weight reduction and dietary recommendations based on individual preferences and what works best to achieve metabolic control in that individual.

Anderson, J. W., Gustafson, N. J., Bryant, C. A., and Tietyen-Clark, J. Dietary fiber and diabetes: a comprehensive review and practical application. *J. Am. Diet Assoc.* 87:1189, 1987; Jenkins, D. J. A., Wolever, T. M. S., Jenkins, A. L., and Taylor, R. H. Dietary fiber, carbohydrate metabolism and diabetes. *Mol. Aspects Med.* 9:97, 1987; Garg, A., Grundy, S. M., and Unger, R. H. Comparison of the effects of high and low carbohydrate diets on plasma lipoproteins and insulin sensitivity in patients with mild NIDDM. *JAMA* 41;1278, 1992; and American Diabetes Association. Nutritional recommendations and principles for people with diabetes. *Diabetes Care* 17:519, 1994.

EXHIBIT B

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

A Fasting Glucose to Insulin Ratio Is a Useful Measure of Insulin Sensitivity in Women with Polycystic Ovary Syndrome

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A Fasting Glucose to Insulin Ratio Is a Useful Measure of Insulin Sensitivity in Women with Polycystic Ovary Syndrome*

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ABSTRACT

Women with polycystic ovary syndrome (PCOS) are profoundly insulin resistant, and the resultant hyperinsulinemia exacerbates the reproductive abnormalities of the syndrome. Agents that ameliorate insulin resistance and reduce circulating insulin levels could provide a new therapeutic modality for PCOS. Identifying the subset of PCOS women who are most insulin resistant may therefore be useful for selecting women who will respond to this therapy. We examined the correlation of basal and oral glucose-stimulated glucose and insulin levels and fasting and stimulated glucose/insulin (G:I) ratios with parameters of insulin sensitivity obtained by frequently sampled iv glucose tolerance test (FSIGT) to assess whether there is a simple screening test for insulin resistance in PCOS. Forty PCOS women (aged 18–40 yr; body mass index, >26 kg/m^2) and 15 control women matched for age, weight, and ethnicity underwent both a 75-g oral glucose tolerance test (OGTT) and a FSIGT. The insulin sensitivity index (S_I) was calculated by application of the minimal model of glucose kinetics to the dynamics of plasma glucose and insulin levels during the FSIGT. The best correlation in PCOS between S_I and a fasting level was found with fasting G:I ratios ($r = 0.73$; $P < 0.0001$). A less substantial, but significant, correlation was found with fasting insulin levels ($r = 0.50$; $P < 0.001$), and no significant correlation was found with fasting glucose levels ($r = 0.24$; P = NS). The fasting G:I was more strongly correlated with S_I than with integrated glucose and insulin responses during the OGTT. The only stronger correlation was with the OGTT 2 h G:I ratio ($r = 0.74$; $P < 0.001$). Stepwise regression analysis with S_I as the dependent variable and fasting glucose and insulin levels, area under the curve for glucose and insulin, and a fasting G:I ratio showed that only the fasting G:I ratio was significantly predictive of S_I in the model (F to remove value = 38.1; $P < 0.001$). When viewed as a screening test for insulin resistance in PCOS, setting a value of the fasting G:I ratio of less than 4.5 as abnormal (using an S_I value below the 10th percentile of our control population as evidence for insulin resistance), the sensitivity of a fasting G:I ratio was 95%, the specificity was 84%, the positive predictive value was 87%, and the negative predictive value was 94%. Receiver operator curve analysis showed that this fasting G:I ratio was the single best screening measure for detecting insulin resistance. We conclude that a fasting G:I ratio may be useful as a screening test for insulin resistance in obese non-Hispanic white PCOS women. This may be a clinically useful parameter for selecting PCOS women most likely to respond to therapeutic interventions that improve insulin sensitivity. (*J Clin Endocrinol Metab* **83**: 2694–2698, 1998)

POLYCYSTIC ovary syndrome (PCOS) is the most common endocrine disorder of premenopausal women, characterized by hyperandrogenic chronic anovulation (1). Women with PCOS are profoundly insulin resistant, and the resulting hyperinsulinemia plays a role in the pathogenesis of the reproductive disturbances (2–4). Abnormalities in insulin action are poorly detected by a single determination of either glucose or insulin levels (5, 6). This diagnosis requires iv administration of glucose, insulin, and/or other substances in a research setting. Such tests are time, labor, and, above all, cost-intensive and are not feasible for large scale screening of populations or routine interval assessment of individuals at risk.

Initial studies have shown that agents that ameliorate insulin resistance and reduce circulating insulin levels, such as troglitazone (7, 8) or metformin (9, 10), may provide a new therapeutic modality in PCOS. Thus, identifying the subset of PCOS women who are the most insulin resistant with a simple test may become more relevant as therapeutic interventions that improve insulin sensitivity in PCOS women are identified. We sought, therefore, to assess whether there was a simple fasting measure of insulin resistance in PCOS women that correlated well with more involved dynamic tests of insulin action.

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Subjects and Methods

Subjects

We studied 40 PCOS and 15 control women. All were non-Hispanic white women from the south central Pennsylvania area. This study was approved by the institutional review board of the Milton S. Hershey Medical Center (Hershey, PA), and all subjects gave written informed consent. The women had a body mass index greater than 26 kg/m^2 and were between 18–40 yr of age. All women were in good health, euthyroid, and, for at least 1 month before each study, were not taking any

medication (except for oral contraceptive agents, which were stopped for 3 months before the study) known to affect sex hormone or carbohydrate metabolism. The diagnosis of PCOS was made by the finding of an elevation of either total testosterone or biologically available testosterone levels associated with chronic oligomenorrhea (6 or fewer menses/yr). Nonclassical 21-hydroxylase deficiency, hyperprolactinemia, and androgen-secreting tumors were excluded by appropriate tests before the diagnosis of PCOS was made. Control women were matched for age, weight, and ethnicity to the women with PCOS. They did not engage in regular aerobic activity, nor did they have a history of diabetes mellitus or hypertension. There was no history of diabetes mellitus in the first degree relatives of the control women. Control women had regular menses every 27–32 days and were not hirsute. Androgen levels in control women were determined without regard to cycle day.

Study protocol

All studies were performed after a 3-day 300-g carbohydrate diet and an overnight fast. Each woman was allowed to rest for 0.5 h after insertion of an iv catheter before the oral glucose tolerance test (OGTT). A 75-g oral glucose load was administered, and blood was obtained for glucose and insulin determinations at 0, 30, 60, 90, and 120 min through the catheter. In two PCOS women we were unable to obtain a sample at 30 min during the OGTT because of technical problems with access. Glucose tolerance was assessed by WHO criteria (11). Forty-three percent of the PCOS women (17 of 40) were glucose intolerant, and all of the control women had normal glucose tolerance.

Insulin action was determined by a frequently sampled iv glucose tolerance test (FSIGT) (12–14). These tests were performed without regard to the phase of the menstrual cycle to assess whether it would still be possible to detect insulin resistance with this simplified study design (14). The FSIGTs were performed after a standard overnight fast of 10 h on a separate day after the OGTT. Women had two iv catheters inserted, one in each arm, and then were allowed to rest for 30 min. At 0 min, 0.3 g/kg glucose was injected over 1 min, and at 20 min, 500 mg tolbutamide (Upjohn Co., Kalamazoo, MI) were injected over 20 s. Blood samples were drawn at −15, −10, −5, −1, 0, 2, 3, 4, 5, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, and 180 min. The insulin sensitivity index (S_I) and glucose effectiveness (S_G; MINMOD computer program version NUDEMM1, R. Bergman, Los Angeles, CA) as well as the acute insulin response to glucose (AIRg) and the disposition index (the product of $S_I \times$ AIRg) were calculated as previously reported (14).

Assays

A single fasting blood sample obtained at 0 min of the OGTT was used for the androgen assays. Assays for testosterone, biologically available, and dehyroepiandrosterone sulfate were performed as previously reported (7). Glucose was measured by the glucose oxidase technique with a Beckman Glucose Analyzer 2 (Fullerton, CA), and insulin levels were measured using Diagnostic Products Corp. kits (Los Angeles, CA) as previously reported (7). The cross-reactivity with proinsulin at the midcurve of the assay is approximately 40%.

Definition of insulin resistance

S_I values from the age-, weight-, and ethnicity-matched control group were used to define the normal distribution; the tenth percentile for S_I was less than 1.12×10^{-4} $min^{-1}/(\mu U/mL)$. We have previously found that this sample size is adequate to define the variance in this normal population (14). Insulin resistance was then defined in PCOS women as an S_I value less than this.

Data analysis

Continuous data were compared between the two groups (PCOS and controls) using unpaired *t* tests. The integrated area under the curve (AUC) analysis for glucose and insulin was determined according to the formula of Tai *et al.* (15). Regression analysis was performed using S_I as the dependent variable and OGTT fasting and stimulated glucose and insulin levels as independent parameters. Stepwise regression analysis was performed with S_I as the dependent variable and fasting glucose and insulin levels, AUC for glucose and insulin, and fasting G:I ratio. Data were analyzed using StatView 4.5 for the Macintosh (Abacus Concepts, Berkeley, CA). Receiver operator curves (ROCs) were created by calculating the sensitivity and specificity of fixed cut-off points of the various parameters examined. Values are reported as the mean ± SD. $P < 0.05$ was considered statistically significant.

Results

The clinical features of the PCOS women and control women are summarized in Table 1. By design, there were no significant differences between the two groups in age or weight. Waist/hip girth ratios were significantly higher in the PCOS women than in the control women (0.84 ± 0.08 *vs.* 0.78 ± 0.05; $P < 0.05$). PCOS women also had significantly higher levels of circulating testosterone (86.2 ± 34.5 *vs.* 33.4 ± 9.7 ng/dL; $P < 0.0001$), biologically available testosterone (31.2 ± 12.5 *vs.* 8.3 ± 3.8 ng/dL; $P < 0.0001$), and dehyroepiandrosterone sulfate (2472 ± 1570 *vs.* 1501 ± 553 ng/mL; $P < 0.001$). Fasting glucose levels did not differ, but PCOS women had significantly higher fasting insulin levels than control women (27.0 ± 18.1 *vs.* 13.3 ± 10.1 μU/mL; $P < 0.001$). S_I was significantly lower in PCOS than in control women [1.81 ± 1.82 *vs.* $4.37 \pm 2.60 \times 10^{-4}$ $min^{-1}/(\mu U/mL)$; $P < 0.0001$].

S_I was most highly correlated with a 2 h G:I ratio (F = 46.7; $P < 0.0001$; Table 2), followed by the fasting G:I ratio (F = 42.0; $P < 0.0001$; Fig. 1). There was a weaker, but significant, correlation between the fasting G:I ratio with the AIRg in PCOS (r = 0.43; F = 8.7; $P < 0.01$) and the disposition index (r = 0.43; F = 8.9; $P < 0.01$), but no correlation with glucose effectiveness (r = 0.01; F = 0.24; P = NS). Stepwise regression analysis with S_I as the dependent variable and fasting glucose and insulin levels, AUC for glucose and insulin, and a fasting G:I ratio showed that only the fasting G:I ratio was significantly predictive of S_I in the model (F to remove value = 38.1; $P < 0.001$).

Fifty-three percent of PCOS women were insulin resistant using the tenth percentile of the normal distribution in our control women as the cut-off value (Table 3). We examined the sensitivity and specificity of various cut-off values for predicting insulin resistance to create ROC curves for OGTT glucose and insulin levels and G:I ratios (Fig. 2). Sensitivity is plotted against 1 − specificity (or the false positive rate). The ideal screening test is one that approaches or reaches the upper left corner of the graph (100% sensitivity and 100% specificity). A test that approximates a coin flip is the diagonal from the lower left to the upper right corner of the graph. This is best illustrated in Fig. 2A by the fasting glucose level, which comes closest to this diagonal and has corresponding poor sensitivity and specificity at the selected cut-off point

TABLE 1. Clinical and biochemical features of study subjects

Parameter	PCOS (n = 40)	Controls (n = 15)	*P*
Age	26.9 ± 5.4	28.7 ± 5.2	NS
BMI	39.0 ± 7.1	37.1 ± 6.2	NS
Waist/hip ratio	0.84 ± 0.08	0.78 ± 0.05	<0.05
T (ng/dL)	86.2 ± 34.5	33.4 ± 9.7	<0.0001
uT (ng/dL)	31.2 ± 12.5	8.3 ± 3.8	<0.0001
DHEA-S (ng/mL)	2472 ± 1570	1501 ± 553	<0.001
Fasting glucose (mg/dL)	90.0 ± 8.4	86.0 ± 10.4	NS
Fasting insulin (μU/mL)	27.0 ± 18.1	13.3 ± 10.1	<0.001

Values are the mean ± SD.

TABLE 2. Metabolic parameters in 40 PCOS women

Parameter	Mean ± SD	r[a]	P
Fasting			
Fasting glucose (mg/dL)	90.0 ± 8.4	0.241	NS
Fasting insulin (μU/mL)	27.0 ± 18.1	0.504	<0.001
Fasting G:I ratio ($mg/10^{-4}$ U)	4.4 ± 1.9	0.725	<0.0001
OGTT			
AUC glucose[b]	17,065 ± 2827	0.534	<0.001
AUC insulin[b]	18,865 ± 9726	0.603	<0.0001
AUC glucose:AUC insulin ratio[b]	1.12 ± 0.49	0.700	<0.0001
2 h G:I ratio	1.00 ± 0.62	0.743	<0.0001

AUC, Area under the curve; OGTT, oral glucose tolerance test; G:I, glucose to insulin.

[a] Correlation with S_I insulin sensitivity on FSIGT is reported with the r and P values.

[b] Thirty-eight women for AUC analysis.

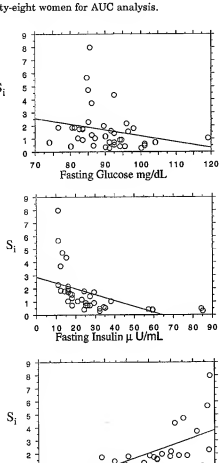

FIG. 1. Regression plots of fasting glucose, fasting insulin, and fasting G:I ratio to S_I (10^{-4} $min^{-1}/(\mu U/mL)$), as determined by FSIGT in PCOS women (n = 40).

(Table 3). The cut-off point for each of the screening tests that has the best combination of sensitivity and specificity is located at the "knee" of the graph and is labeled for each parameter (Fig. 2, A–C).

The fasting G:I ratio (Fig. 2A) provided the best single fasting measure of insulin action and was comparable to glucose-stimulated parameters (Fig. 2B). A fasting G:I ratio (cut-off value, <4.5) provided the best combination of sensitivity (95%) and specificity (84%) as well as the best positive predictive value (87%) and negative predictive value (94%) as a screening test for predicting insulin resistance in PCOS (Table 3). This was similar for the lower limits of the 95% confidence intervals for the fasting G:I ratio. The next best single predictor of insulin resistance was the fasting insulin level. The glucose-stimulated parameters obtained from the OGTT, although sensitive, displayed less specificity than the fasting insulin and/or the fasting G:I ratio (Table 3).

Discussion

Our results indicate that a fasting G:I ratio is a good measure of insulin sensitivity in obese PCOS women and has both high sensitivity and specificity for detecting insulin-resistant women. Fasting hyperinsulinemia has been used as a measure of insulin action (5, 6). Basal and glucose-stimulated hyperinsulinemia are well reported in obese PCOS women (2, 16). This is secondary to profound peripheral insulin resistance (4, 14). Fasting glucose levels are also higher in obese PCOS women secondary to increased basal hepatic glucose production (4, 17), which reflects hepatic insulin resistance, but this usually does not achieve statistical significance, as is the case in the present study. The fasting G:I ratio reflects both of these abnormalities and could be predicted to be a more sensitive marker for insulin resistance than either value alone, consistent with our findings. The fasting G:I ratio would not be predicted to be a good measure of insulin resistance in nonobese PCOS women because they have neither fasting hyperinsulinemia (3, 4, 16) nor increased basal hepatic glucose production (4, 17). As nonobese PCOS women were not included in the present study, we can not directly confirm this.

Insulin resistance and the resulting hyperinsulinemia contribute to the reproductive abnormalities of PCOS women (2, 18). Lowering circulating insulin levels by a variety of mechanisms has resulted in decreased androgen levels in PCOS women. As little as a 7% decrease in body weight has significantly improved hyperandrogenism (19). The short term use of agents that lower insulin secretion, such as diazoxide or somatostatin, produces similar effects (20, 21). Therapy with metformin, which acts primarily by suppressing hepatic gluconeogenesis, when accompanied by a reduction in circulating insulin levels, can decrease androgen levels in PCOS (9, 10, 22). In two small studies, the administration of troglitazone, an agent that directly reduces target tissue insulin resistance and, accordingly, circulating insulin levels, also resulted in a decrease in circulating androgen levels in PCOS women (7, 8). A baseline fasting G:I ratio has been shown to have good correlation with the clinical efficacy of troglitazone on hyperglycemia in Japanese patients with type 2 diabetes (23).

We have chosen the lower decile of insulin sensitivity from an age-, weight-, and ethnicity-matched control group to define insulin resistance. If we had selected a less stringent criterion that reflects the prevalence of insulin resistance in the larger population (24), such as a value below the 25th

TABLE 3. Sensitivity, specificity, positive predictive value, and negative predictive value (including 95% confidence intervals) of parameters of insulin resistance as defined by S_I (below the 10th percentile of obese controls) in 40 women with PCOS

Parameter	Value	Graph point	% Sensitivity (n) [95% CI]	% Specificity (n) [95% CI]	% Positive predictive value (n) [95% CI]	% Negative predictive value (n) [95% CI]
Fasting values						
Glucose (mg/dL)	≥90	A	71 (15/21) [52–90]	68 (13/19) [47–89]	71 (15/21) [52–90]	68 (13/19) [47–89]
Insulin (μU/mL)	≥20	B	90 (19/21) [77–100]	84 (16/19) [68–100]	86 (19/22) [72–100]	89 (16/18) [75–100]
Fasting G:I ratio (mg/10^{-4} U)	<4.5	C	95 (20/21) [86–100]	84 (16/19) [68–100]	87 (20/23) [73–100]	94 (16/17) [83–100]
Glucose-stimulated values						
2 h G:I ratio	<1.0	D	95 (20/21) [86–100]	63 (12/19) [41–85]	74 (20/27) [57–91]	92 (12/13) [77–100]
AUC insulin[a]	≥15,500	E	84 (16/19) [68–100]	74 (14/19) [54–94]	76 (16/21) [58–94]	82 (14/17) [64–100]
AUC glucose[a]	≥15,400	F	95 (18/19) [85–100]	58 (11/19) [36–80]	69 (18/26) [51–82]	92 (11/12) [77–100]
AUC glucose/AUC insulin ratio[a]	<1.0	G	90 (16/19) [77–100]	68 (12/19) [47–87]	70 (16/23) [51–89]	80 (12/15) [60–100]

The graph point chosen as the cut-off point is based on the ROC curves in Fig. 2.
G:I, Glucose to insulin; AUC, area under the curve; OGTT, oral glucose tolerance test; n, number detected/total number in the category.
[a] Thirty-eight women in AUC analysis.

percentile of the control population, 80% of PCOS women would have been designated insulin resistant. For the purposes of evaluating the usefulness of the fasting G:I ratio as well as other OGTT parameters as screening tests for insulin action, we used the more stringent criterion of the lowest decile of insulin sensitivity as the cut-off point. Other groups have defined insulin resistance as a measure of insulin action in the lower decile of insulin sensitivity in lean subjects (25). By using obese women to define the normal range of insulin sensitivity, we were assessing insulin resistance that was beyond that due to obesity *per se*.

A brief report by Parra and colleagues suggested that a fasting G:I ratio might be a useful measurement for predicting glucose-stimulated hyperinsulinemia in PCOS women (26). We have shown for the first time that the fasting G:I ratio is a sensitive and specific marker of insulin sensitivity in PCOS. S_I as determined by FSIGT has been shown to be highly correlated with insulin action determined by the euglycemic glucose clamp technique in many insulin-resistant states, including PCOS (27, 28). We have also controlled for the effects of age, weight, and ethnicity in PCOS women on insulin sensitivity by using an appropriate control group (4, 29–31).

We chose ROC curve analysis to graphically portray the trade-off involved in improving a test's sensitivity at a cost of lower specificity and to select the best cut-off value. The fasting G:I ratio offered the best single cut-off measure (including sensitivity, specificity, positive predictive value, negative predictive value, and 95% confidence intervals), had a better correlation with S_I by simple regression than fasting insulin level, and was a better fasting predictor of S_I by our stepwise regression model. We do not have an adequate sample size to assess statistically whether the fasting G:I ratio is superior to a fasting insulin level by comparison of ROC AUC analysis. A power analysis based on our preliminary findings suggests that we would need 4 times as many PCOS women in the insulin-resistant group to detect a difference in the sensitivity of the two measures.

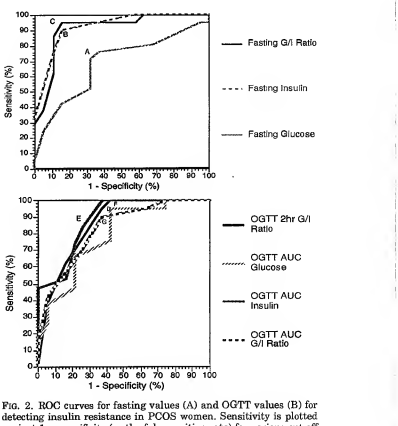

FIG. 2. ROC curves for fasting values (A) and OGTT values (B) for detecting insulin resistance in PCOS women. Sensitivity is plotted against 1 – specificity (or the false positive rate) for various cut-off values. The ideal test is one that approaches or reaches the upper left corner of the graph (100% sensitivity and 100% specificity). A test that approximates a coin flip yields a diagonal from the lower left to the upper right corner of the graph. The cut-off point that has the best combination is located at the "knee" of the graph and is labeled for each parameter (A–G). The cut-off values of the test are given in Table 3.

Our results indicate that a fasting G:I ratio is an easily obtainable, safe, highly sensitive, and specific measure of insulin sensitivity in obese non-Hispanic white PCOS women. The predictive power of both a positive and a negative test is excellent. Further studies will be needed to validate this measure in other populations. We suggest that the fasting G:I ratio may be a useful test for identifying PCOS women with insulin resistance. These women may be more likely to benefit from therapies that lower circulating insulin levels.

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